[Frontiers in Bioscience, Landmark, 18, 91-105, January 1, 2013]

Scratching the surface: signaling and routing dynamics of the CSF3 receptor

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1. ABSTRACT

Following activation by their cognate ligands, cytokine receptors undergo intracellular routing towards lysosomes where they are degraded. Cytokine receptor signaling does not terminate at the plasma membrane, but continues throughout the endocytotic pathway. The modes of internalization and intracellular trafficking of specific receptors, the level of recycling towards the plasma membrane, the type of protein modifications (phosphorylation, ubiquitination) and the enzymes involved in these processes are remarkably diverse. This heterogeneity may contribute to the fine-tuning of signal amplitudes and duration from different receptors. The colony-stimulating factor 3 receptor (CSF3R) is unique for its balanced signaling output, first leading to proliferation of myeloid progenitors, followed by a cell cycle arrest and granulocytic differentiation. The mechanisms associated with CSF3R signal modulation, involving receptor lysine ubiquitination and redox-controlled phosphatase activities, are to a large extent confined to the signaling endosome. Interactions between signaling endosomes and the endoplasmic reticulum play a key role in this process. Here, we review the mechanisms of intracellular routing of CSF3R, their consequences for myeloid blood cell development and their implications for myeloid diseases.

2. CSF3 AND ITS RECEPTOR (CSF3R)

Granulocyte colony stimulating factor, now termed colony-stimulating factor 3 (CSF3) and its receptor (CSF3R) control neutrophil production under basal and bacterial infection-driven "emergency" conditions (1, 2). CSF3 induces proliferation of myeloid progenitor cells, which then proceed in differentiation towards neutrophilic granulocytes. In addition, CSF3 enhances neutrophil effector functions such as superoxide generation, production of leukocyte alkaline phosphatase, myeloperoxidase and release of arachidonic acid (3, 4, 5). CSF3 or CSF3R deficient mice are severely neutropenic and hyper susceptible to infections, confirming the nonredundant role of CSF3 in granulopoiesis and host defense (6, 7). CSF3R, a member of the hematopoietin receptor superfamily (8, 9), is a single transmembrane protein consisting of 813 amino acids, of which 603 amino acids form the extracellular domain (10, 11). The extracellular portion consists of an immunoglobulin-like (Ig-like) domain, a cytokine receptor homology domain (CRH domain) and three fibronectin type III (FNIII) modules. The cytoplasmic domain of the CSF3R contains the conserved membrane proximal box 1 and box 2 regions involved in the transduction of proliferation signals (12, 13). The CSF3R forms a 2:2 complex with its ligand CSF3, resulting in the homodimerization of the CSF3R (14).

The hematopoietin superfamily of receptors lack intrinsic tyrosine kinase activity but activate one or multiple members of the Janus tyrosine kinases (JAK) family. The CSF3R activates three members of the JAK family, JAK1, JAK2 and TYK2 which bind to the juxtamembrane cytoplasmic region of the CSF3R (15, 16, 17, 18, 19, 20). The cytoplasmic domain of CSF3R contains four conserved tyrosine (Y) residues, which upon phosphorylation serve as docking sites for Src homology 2 (SH2) domain-containing signaling proteins, including signal transducer and activator of transcription 3 (STAT3), suppressor of cytokine signaling (SOCS)3, the SH2-containing tyrosine phosphatase Shp2 and the adaptor proteins Shc and Grb2. Although dispensable for G-CSF-induced granulopoiesis, these pY-coupled pathways orchestrate the signaling output of CSF3R, thereby controlling the proliferation/differentiation balance in neutrophil development under basal and "emergency" granulopoiesis (21). Details of the pY-linked signaling pathways activated by CSF3R have been reviewed earlier (22, 23). Another structural feature of the CSF3R cytoplasmic domain is that it contains conserved lysine residues that are target for ubiquitination. As will be discussed below, one of these lysines plays a crucial role in intracellular routing of CSF3R, both in the biosynthetic (anterograde) and endocytotic (retrograde) pathways.

CSF3 is commonly applied in the clinic to alleviate neutropenia in a variety of conditions and is administered to healthy stem cell donors to mobilize hematopoietic stem cells into the periphery. Acquired mutations in CSF3R have been detected in patients with a severe form of congenital neutropenia, a defect that is associated with an increased risk of developing acute myeloid leukemia (AML) (24, 25, 26). These nonsense mutations result in the truncation of a C-terminal region of the CSF3R protein that contains multiple regulatory motifs, responsible for receptor internalization and signal attenuation by the suppressor of cytokine signaling 3 (SOCS3). The signaling properties of the truncated CSF3R are severely perturbed, leading to elevated proliferative and reduced differentiation responses of myeloid progenitors to CSF3 (22, 24).

3. MECHANISMS CONTROLLING INTRACELLULAR ROUTING OF CSF3R

Newly synthesized receptors are exported from the endoplasmic reticulum (ER) towards the plasma membrane, passing sequentially through the ER-Golgi intermediate compartment, the Golgi and the trans-Golgi network. During this process, receptor proteins undergo maturation and folding owing to post-translational modifications (27, 28), whereas not properly matured and misfolded proteins undergo ER-associated degradation (29). Relative to the total intracellular pool, only a small fraction of CSF3Rs are expressed on the membrane, suggesting that a tightly controlled equilibrium exists between the portion of newly synthesized CSF3Rs transferred to the plasma membrane and the intracellular fraction that is either stored for transport to the plasma membrane or targeted for degradation. Supporting this idea, the pool of intracellular CSF3Rs has been predominantly associated with the Golgi and lysosome compartments (30).

3.1. Ubiquitin dependent mechanisms of forward trafficking

Ubiquitination on lysine residues is the major protein modification implicated in intracellular traffic and subsequent targeting for proteasomal or lysosomal degradation (31, 32). The CSF3R contains 5 conserved lysines in its cytoplasmic domain that can serve as potential target for ubiquitination. Mutational analysis revealed that the most juxtamembrane lysine (located at a.a. position 632) is a crucial determinant of cell surface expression of CSF3R, even though other lysine residues are also ubiquitinated (33). Importantly, as will be discussed later in this review, this membrane proximal lysine is also critical for lysosomal routing of ligand-activated CSF3R in the retrograde pathway. The ubiquitin ligase c-Cbl has been implicated in ubiquitination and Ub-mediated intracellular routing of the EGF receptor and several other intrinsic tyrosine kinase receptors. In contrast, there is little evidence for a universal role c-Cbl in the routing of cytokine receptors, suggesting that other E3 ligases are involved. Yeast-two-hybrid and mammalian protein-protein interaction analysis showed that the WD40-repeat and SOCS-box containing proteins WSB1 and 2, first identified by Hilton and colleagues (34) bind to the distal part of the CSF3R (35). Subsequent functional studies showed that WSB proteins indeed can act as E3 ligase complexes that ubiquitinate CSF3R, resulting in reduced routing to the plasma membrane and increased lysosomal degradation (35). This activity was fully dependent on the critical lysine residue 632 in the CSF3R and on the integrity of the SOCS box of WSB, the domain critical for its E3 ligase activity (35). More recently, WSB proteins have also been implicated in both forward and retrograde routing of the IL-21 receptor (36, 37). However, it remains to be investigated whether WSB proteins are more generally involved in controlling cytokine receptor traffic. Another E3 ligase implicated in plasma membrane expression of a cytokine receptor is ring finger protein 41 (RNF41), which decreases erythropoietin receptor (EPOR) levels and attenuates EPO-induced differentiation of multipotent EML cells (38). RNF41 also controls expression and degradation of the leptin receptor (39). Clearly, we are still just at the brink of unraveling the roles of different E3 ligase systems in the control of cytokine receptor traffic and likely there will be cell type specificity and redundancy between different E3 ligases in play. It must also be kept in mind that most studies reported thus far have been performed in cell line models and that their significance for cytokine responses *in vivo* still needs to be determined.

3.2. JAKs and CSF3R plasma membrane expression

Besides being essential for signal transduction, JAKs have more recently also been shown to increase the cell surface expression of certain cytokine receptors, independent of their kinase activity (40). In line with these findings, ectopic expression of JAK1, JAK2 or TYK2 significantly enhanced CSF3R cell surface expression, depending on the presence of a critical tryptophan (W650) in the juxtamembrane region of CSF3R that is crucial for

JAK binding (20). Two potential explanations for the elevated expression of CSF3R at the plasma membrane are that (i) JAKs inhibit the constitutive (i.e., ligand independent) internalization of CSF3R from the plasma membrane or (ii) mask the lysine-containing motif implicated in quality control and proteasomal/lysosomal degradation of the receptor protein in the biosynthetic pathway. However, JAKs neither masked motifs essential for constitutive CSF3R internalization nor caused reduced ubiquitination of the CSF3R (33), leaving the underlying mechanism of JAK-induced CSF3R stability and cell surface expression elusive. Strikingly, concomitant expression of JAK2 and the lysine-less CSF3R mutant K5R or the d715 truncation mutant prevented apoptosis of IL-3 dependent Ba/F3 cells after growth factor deprival (33). These findings illustrate how elevated JAK levels, in combination with routing defects owing to the loss of CSF3R ubiquitination or defective internalization, may contribute to uncontrolled cell survival in the absence of growth factor (33). However, to what extent JAK proteins expressed at physiological levels contribute to quality control and receptor trafficking to the plasma membrane is controversial, at least for the EPOR (41). Also for the CSF3R, the influence of endogenous JAKs on plasma membrane expression appears to be minor or absent, since no difference was noted between the cell surface expression of the CSF3R W650 mutant (not able to bind JAKs) and the wild type CSF3R in cells not overexpressing JAKs (33). In conclusion, when expressed at high levels in cell line models, JAKs associate with the CSF3R in the biosynthetic pathway and protect CSF3R from degradation, but whether this occurs under physiological conditions remains uncertain.

3.3. CSF3R in the retrograde pathway

The role of receptor endocytosis, subsequent trafficking to sorting endosomes, late endosomes and lysosomes in relation to cell signaling has received major attention and has been the subject of recent reviews (42, 43, 44, 45). Most of our current knowledge of these processes, including the involvement of components of the endosomal sorting complex required for transport (ESCRT) machinery is derived from studies of receptor tyrosine kinases (RTKs), particularly the epidermal growth factor receptor (EGFR) (42, 43, 44, 45, 46). Ubiquitination of the EGFRs, resulting in the interaction with multiple ubiquitin-binding adaptor proteins, plays a key role in the intracellular routing of EGFR (47, 48, 49, 50, 51, 52). The ring finger protein c-Cbl is the major E3 ligase involved in EGFR ubiquitination and EGFR mutants lacking either the Cbl-binding site or critical lysines in the cytoplasmic region are severely hampered in their traffic from early towards late endosomes, leading to delayed and reduced lysosomal degradation (53, 54).

A role for c-Cbl in CSF3R signaling has been reported, but its proposed mode of action differs from that described for the EGFR: rather than playing a role as an E3 ligase involved in ubiquitination and retrograde routing, c-Cbl has been suggested to act as a docking molecule between the Src kinase Lyn and phosphoinositide-3 kinase (PI-3K), thereby enhancing Lyn-dependent proliferative signaling in cell lines derived from DT40 B cells (55, 56). A role for c-Cbl in ubiquitination and lysosomal or proteasomal degradation has been demonstrated for some receptors of the cytokine receptor superfamily, i.e., the thrombopoietin receptor (c-Mpl), the IL-6 receptor signaling subunit gp130 and the common cytokine receptor g chain (57, 58, 59). However, c-Cbl is not the only E3 ligase implicated in ubiquitination and lysosomal trafficking of cytokine receptors and several studies have identified alternative E3 ligase systems involved in this process. For instance, after activation of the EPOR, the Skp, Cullin and F-box beta-Transducin repeat containing protein (beta-Trcp) complex SCF binds to the receptor, causing receptor ubiquitination and degradation (60). Besides beta-Trcp another E3 ligase, i.e., receptor-associated ubiquitin ligase (RUL) interacts with the EPOR. RUL ubiquitinates EPOR, but its involvement in EPOR degradation has not been demonstrated (61). beta-Trcp also ubiquitinates the activated IFNAR on a cluster of lysine residues, which is required for internalization and lysosomal targeting of the receptor (62). Beta-Trcp preferentially conjugates ubiquitin to lysine residues located 9–13 amino acids upstream of the ligase recognition site (63), which exposes a linear motif that promotes IFNAR endocytosis (64, 65). Beta-Trcp also drives endocytosis and lysosomal degradation of the prolactin receptor and growth hormone receptor (GHR). Strikingly, in view of its dependence on the ubiquitin system and β-Trcp, receptor lysines are fully dispensable for endocytotic routing of GHR, suggesting that adapter molecules are involved in this process that need to be ubiquitinated (66).

CSF3R does not contain a consensus substrate motif for beta-Trcp and thus far no evidence has been obtained that either beta-Trcp, c-Cbl or RUL are involved in lysosomal routing of CSF3R (67). Instead, the E3 ligase activity of suppressor of cytokine signaling 3 (SOCS3) has been suggested to play a major role in this process (Figure 1). SOCS3 expression is directly controlled by STAT3, the major STAT protein activated by CSF3 (68, 69, 70). SOCS3 protein is then recruited to phosphorylated tyrosine residue 729 (pY729) of the activated CSF3R (68) and attenuates signaling in a classical negative feedback loop. SOCS3 has two distinct domains modulating CSF3 signaling, the kinase inhibitory region (KIR) and the SOCS box (71, 72, 73, 74). While the inhibitory action of the KIR on JAK activity has been clearly demonstrated, the role of the SOCS box initially remained less clear. A negative regulatory role of the SOCS box on CSF3 signaling was demonstrated both *in vitro* and *in vivo*, the latter in a targeted mouse model specifically lacking the SOCS3-SOCS box (75, 76). These SOCS3-deltabox mice have normal neutrophil levels under basal conditions, but significantly elevated absolute neutrophil counts relative to wild type littermates after CSF3 administration, suggesting that CSF3-induced emergency granulopoiesis is attenuated by SOCS3 through the activity of the SOCS box (75). The SOCS box interacts with the Elongin B/C, Cullin 5, and RING finger protein Rbx2 complex that acts as an E3 ubiquitin ligase (77). While JAKs are generally considered as the prime substrates for SOCS-mediated ubiquitination

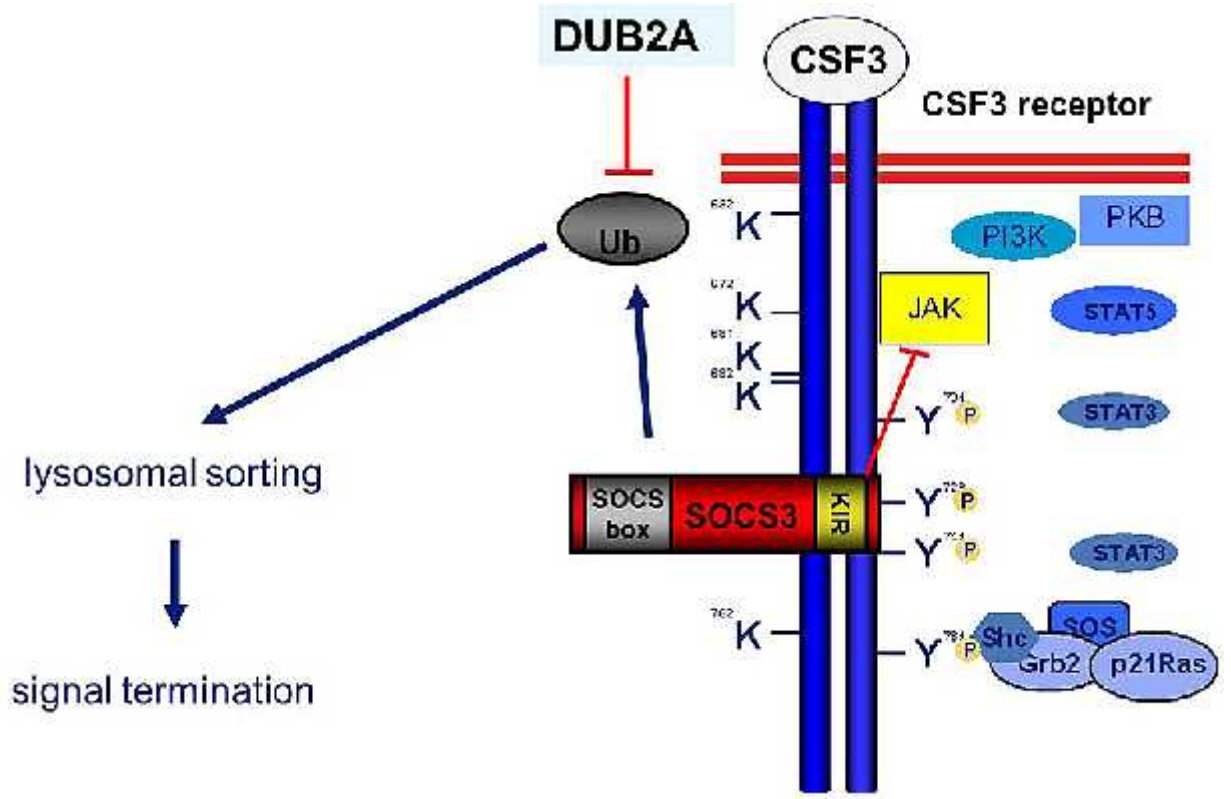

Figure 1. SOCS3 and DUB2-mediated lysosomal routing of CSF3R involving the critical membrane proximal lysine CSF3R-K632. After activation of STAT3, expression of SOCS3 is induced. SOCS3 will then bind to a phosphorylated tyrosine (Y729) motif of CSF3R, most likely when the activated receptor is in transit from the plasma membrane towards the early endosome/signaling endosome. In addition to attenuating JAK activity through its kinase inhibitory region (KIR), E3 ligase activity recruited through the SOCS box mediates ubiquitination of K632, which is indispensable for routing from early to late endosomes/lysosomes. DUB2A, also induced by CSF3, counteracts this process by deubiquitinating CSF3R residing in the early endosomes.

and proteasomal degradation, the fact that SOCS3 binds to pY729 of CSF3R raised the possibility that CSF3R itself might be a SOCS3 substrate. In support of this, it was shown that SOCS3 enhances the ubiquitination of the membrane proximal lysine residue K632 of CSF3R. Mutation of this lysine, conserved among a number of cytokine receptors, affects CSF3R trafficking from early to late endosomes, resulting in prolonged STAT5 activation and enhanced cell proliferation (78). Mutational analysis further showed that the position of this lysine to drive lysosomal routing is somewhat flexible. However, its juxtamembrane localization appeared crucial, since neither fusion of ubiquitin to the C-terminus nor reallocating the juxtamembrane domain to the C-terminus could induce routing of the lysine-less CSF3R-K5R from early towards late endosomes (67). These observations imply that CSF3R-K632 is not part of a linear sorting motif and suggest that proximity of an ubiquitinated lysine to the membrane is essential for the interaction with downstream sorting proteins. These remain to be identified but candidate proteins known to play an essential role in sorting of receptors to late endosomes and lysosomes are Epsin, Hrs and EAP45 (79, 80, 81).

3.4. Deubiquitinating enzymes involved in CSF3R routing

Protein ubiquitination is antagonized by deubiquitinating enzymes (DUBs). Two endosomal DUBs, associated molecule with the SH3 domain of STAM (AMSH) and ubiquitin isopeptidase Y (UBPY) are involved in routing of activated receptors. Both bind to the ESCRT-0 subunit STAM1 via their SH3 domain and to ESCRT-III through their microtubule interacting and transport domains (82, 83, 84, 85). AMSH is implicated in endosomal trafficking of multiple tyrosine kinase receptors, e.g., the EGFR, and G-protein coupled receptors like protease activated receptor 2, delta-opioid peptide receptor and CXCR4 (86, 87, 88, 89). UPBY is also essential for deubiquitination and degradation of these receptors (87, 88, 90) and has been proposed to maintain the pool of free ubiquitin by releasing it from the cargo just prior to their lysosomal degradation (91). Although AMSH and UBPY both deubiquitinate CSF3R, neither of the enzymes increased protein stability of CSF3R, indicating that they do not effectively prevent lysosomal targeting (92). A family of DUBs comprising of DUB1, DUB1A, DUB2 and DUB2A, was previously shown to be induced by different cytokines (93, 94, 95, 96). One family member, DUB2A is

upregulated in response to CSF3 stimulation in myeloid cells (92). DUB2A is 97% identical to DUB2 and reduces the ubiquitination of CSF3R, leading to its accumulation in early endosomes and enhanced stability (92). DUB2 has been reported to play a similar role in the control of the common g chain of interleukin receptors (57). Whether DUB2 directly deubiquitinates CSF3R or (also) acts indirectly through deubiquitination of CSF3R-associated proteins or proteins of the endocytotic machinery is currently unknown. For instance, DUB1, a highly related family member, deubiquitinates dynein heavy chain (97), which associates with microtubule complex (98). Because dynein is involved in the movement of late endosomes along microtubules, receptor sorting and morphogenesis of early endosomes it is possible that deubiquitination of dynein may also affect receptor protein stability (99, 100). However, whether this applies to CSF3R still needs to be addressed. Currently, we propose a model in which DUB2A attenuates routing of CSF3R from early to late endosomes by interfering with SOCS3-mediated ubiquitination of the critical membrane proximal K632 of CSF3R (Figure 1).

4. ROLE OF PHOSPHATASES RECRUITED TO THE ACTIVATED CSF3R AT THE PLASMA MEMBRANE

The SH2-containing protein tyrosine phosphatase Shp1, encoded by Ptpn6, negatively controls CSF3R signaling via a still unknown mechanism (101, 102, 103). Shp1 is a cytosolic protein that is recruited to activated growth factor receptors at the plasma membrane (104), but has also been detected in the nucleus (105). Mice carrying a loss of function mutation in Ptpn6 display myeloid as well as lymphoid abnormalities. Interaction of Shp1 with CSF3R does not depend on cytoplasmic tyrosines of the CSF3R (106, 107, 108). The expression of Shp1 rises with CSF3-induced differentiation in 32D cells. Overexpression of Shp1 inhibits proliferation and stimulates differentiation, while a catalytically inactive Shp1 has the opposing effect and inhibits differentiation and stimulates proliferation in 32D cells (108). Shp2, encoded by Ptpn11, is predominantly a cytosolic protein translocating to activated receptors at the plasma membrane (104). Shp2 competes with SOCS3 for binding to pY729 of the CSF3R (70). Furthermore, Shp2 binds to Y704 and Y764 of the CSF3R via its interaction with Grb2 (109). Similar to Shp1, it is still largely unclear which signaling proteins activated by CSF3R are the key substrates for Shp2's phosphatase activity; one of the proposed substrates is STAT5 (110). Notably, an alternative role of Shp2 has been proposed, in which the Src kinase Lyn, recruited to pY764 of CSF3R via Grb2/Gab2 docking proteins is a substrate for dephosphorylation (111). Finally, Shp2 also enhances Ras/Erk signaling, by acting as an adaptor protein that recruits Grb2 bound to Son of sevenless (Sos) a major nucleotide exchange factor for Ras (112). The inositol-5 phosphatase Ship1, recruited via pY764 of the CSF3R (113, 114, 115), inhibits granulopoiesis, as is e.g., evident from the elevated numbers and prolonged survival of neutrophils in Ship1-/- mice (116, 117). The above-mentioned examples indicate that multiple protein tyrosine and lipid phosphatases, recruited to the CSF3R complex at the plasma membrane, fine-tune the response of myeloid progenitors to CSF3, both under basal conditions and during episodes of bacterial infections. However, as will be discussed in more detail below, another major phosphatase involved in the control of CSF3R signaling acts predominantly from the endoplasmic reticulum (ER), from where it modulates the signaling function of CSF3Rs that reside in early (signaling) endosomes.

5. ROLE OF THE ER-RESIDENT PROTEIN TYROSINE TYROSINE PHOSPHATASE PTP1B IN CSF3R SIGNALING

Ptp1b is prototypic of the family of protein tyrosine phosphatases and its role in metabolism and associated diseases (obesity and diabetes) and cancer has received major attention (118). Major RTKs affected in their signaling by Ptp1b include the insulin receptor (IR), platelet-derived growth factor receptor (PDGFR), insulin-like growth factor 1 receptor, and the EGFR. The main function of Ptp1b in the context of insulin receptor is receptor dephosphorylation. Importantly, the site of regulation of RTKs by Ptp1b is not at the plasma membrane, but at the ER, where Ptp1b resides with its catalytic domain exposed towards the cytoplasm and where it may keep RTKs in the biosynthetic pathway in an inactive state (119, 120). In elegant studies using fluorescence lifetime imaging microscopy and electron microscopy it was demonstrated that activated and endocytosed EGFR and PDGFR encounter the ER-resident Ptp1b, 10 to 30 minutes after stimulation with the respective growth factors (121, 122).

The effects of Ptp1b are not restricted to RTKs but extend to some cytokine receptors that activate JAK/STAT signaling. To exactly which receptor systems this applies and at what level(s) JAK/STAT activation by these receptors is regulated by Ptp1b still remains to be fully explored, but the data available thus far suggest that this may be diverse. For instance, in case of the leptin receptor, it was suggested that the effects of Ptp1b are predominantly mediated by dephosphorylating JAK2, a result supported by substrate trapping experiments (123, 124). Studies on the prolactin and IL4 receptors provided evidence that Ptp1b is involved in the inactivation of STAT5 and STAT6 complexes, respectively (125, 126). EPOR was shown to directly interact with Ptp1b in BOSC-23T cells and loss of Ptp1b expression resulted in increased phosphorylation of tyrosines of EPOR (127). Ptp1b also attenuates signaling from CSF3R. A recent study using Ptp1b deficient bone marrow cells showed that Ptp1b inhibits CSF3-induced activation of JAK2 and STAT3 and proliferation of myeloid progenitors in colony assays. In contrast, responses to CSF2 (GM-CSF) were insensitive to Ptp1b (128). Confocal microscopy and *in situ* proximity ligation assays established that ligand-activated CSF3R and Ptp1b physically interact at the ER-early endosome interface. Furthermore, loss of Ptp1b resulted in prolonged tyrosine phosphorylation of CSF3R, implying that Ptp1b attenuates interactions with SH2-containing signaling proteins (128). These findings show that signal modulation

by phosphatases does not only take place at the plasma membrane but may also occur as a result of intracellular traffic and encounter of signaling endosomes with intracellular organelles such as the ER.

6. REDOX-CONTROLLED MECHANISMS OF CSF3R SIGNALING

Cysteine residues in the catalytic sites of phosphatases are prone to oxidation, which inhibits their enzymatic activity (129, 130, 131). Ptp1b is sensitive to oxidation by reactive oxygen species (ROS) and is therefore considered a major target for redox-controlled signaling (131). The NADPH oxidase (Nox) systems are major producers of ROS and have been implicated in a wide variety of physiological processes and disease states (132). The localization of different Nox complexes is thought to contribute to the sub-cellular confinement of ROS mediated responses. For instance Nox2, localized in proximity of the plasma membrane, was shown to translocate to the early endosomes upon activation of IL-1R and to control recruitment of TRAF6 to the IL1R/MyD88 complex (133). Nox4, on the other hand, is localized at the ER (27, 134), and inhibition of Ptp1b activity by insulin has been attributed to Nox4-mediated ROS production (135, 136). In the context of the IL-4R, ER-associated Nox1 and Nox5L have been suggested to be responsible for inactivation of Ptp1b (137).

Peroxiredoxins (Prdx) are a family of antioxidant proteins, of which some members (Prdx 1 and 2) have been implicated in the control of RTK signaling. Peroxiredoxin 2 (Prdx2) physically interacts with PDGFR and the active site of Prdx2 was shown to be critical for negative regulation of PDGFR mediated signaling (138). Prdx1 has a similar effect, but intriguingly, Prdx1 appears to be negatively controlled by tyrosine phosphorylation through the PDGFR (and EGFR) (139). Based on these findings, a model has been proposed in which the temporary reduction of Prdx1 activity by receptor-mediated phosphorylation causes a localized H2O2 accumulation in proximity of the plasma membrane. This then leads to a transiently elevated signaling output owing to oxidation and reduced activity of phosphatases, likely including the lipid phosphatase PTEN (139). Intriguingly, not Prdx1 or Prdx2, but another family member, Prdx4, was found to interact with the activated CSF3R (128). Prdx4 is predominantly localized in the ER (140) and its anti-oxidant activity will therefore preferentially inhibit oxidation of ER-resident or proximal phosphatases, including Ptp1b (Figure 2). Supporting this idea, CSF3 responses of Prdx4 deficient bone marrow cells were comparable to those of Ptp1b-/- mice, i.e., giving rise to significantly more and larger colonies in CFU-G assays (128). These findings add to the concept that the ER has an important regulatory function in growth factor receptor signaling and identify the control of ROS levels as yet another major determinant of signal modulation at the ER-early endosome interface. As will be discussed below, this has ramifications for CSF3R mutants found in severe congenital neutropenia that are hampered in intracellular trafficking.

7. SPATIO-TEMPORAL ASPECTS OF CSF3R SIGNALING

Our current view of how receptor endocytosis and endosomal trafficking of CSF3R contributes to signal duration and diversification can be summarized as follows: After ligand activation at the plasma membrane, JAKs phosphorylate STATs and the tyrosine-based docking sites for the SH2-containing molecules STAT3, SOCS3, Shp2 and the docking proteins Shc and Grb2 involved in PI-3K/Akt and Ras/Erk activation (Figure 1). The phosphatases Shp1, Shp2 and Ship1, will be recruited to the activated receptor at this stage, thereby controlling its signaling from the plasma membrane. Following ligand-induced endocytosis, receptors arrive in early endosomes, approximately 10-15 min after CSF3 activation, where PI-3K/Akt signaling is switched off (30). This is most likely caused by the physical separation between PIP-bound Akt, retained at the plasma membrane from CSF3R residing in early endosomes (Jevdjovic *et al*, manuscript in preparation). In contrast to Akt, activation of STAT3, STAT5 and Erk by CSF3R continues from early endosomes, which then become subject to control by ER-resident Ptp1b, kept in an active state by the antioxidant protein Prdx4, and SOCS3-driven ubiquitination and lysosomal degradation of CSF3R, a process counterbalanced by the deubiquitinating enzyme DUB2A (Figure 2). Finally, it was recently shown that transition of CSF3R from late endosomes to lysosomes is controlled by yet another mechanism involving sequestosome 1 (SQSTM1), a protein previously implicated in autophagy. Possibly, SQSTM1 abrogates CSF3-induced Erk activation at the late endosome-lysosome transit, either by degradation of CSF3R, degradation of the scaffolded Erk complex associated with late endosomes, or a combination of both (141).

8. ABNORMAL CSF3R SIGNALING IN MYELOID DISORDERS

The two myeloid disorders in which abnormal CSF3R function has been implicated are severe congenital neutropenia (SCN) and acute myeloid leukemia (AML) (22). SCN patients receive CSF3 treatment to alleviate neutropenia and related mortality and morbidity due to opportunistic bacterial infections. However, some patients progress to AML under CSF3 treatment (24). Leukemic transformation is frequently accompanied by the acquisition of nonsense mutations in CSF3R that truncate the C-terminal region (~100 amino acids) of the CSF3R (24). The consequences of these truncations are multi-fold: they affect receptor endocytosis, forward and retrograde receptor traffic, signal attenuation by SOCS3 and redox control of signaling.

Specifically, the CSF3R truncation mutants, with d715-CSF3R as the prototype, (i) lack a dileucine-based motif resulting in attenuated internalization, (ii) lack the SOCS3 recruitment site Y729, resulting in defective inhibition of JAK activation and CSF3R ubiquitination (67), (iii) lack the interaction with Prdx4/Ptp1b at the ER interface, (iv) lack the interaction with WSB, resulting in

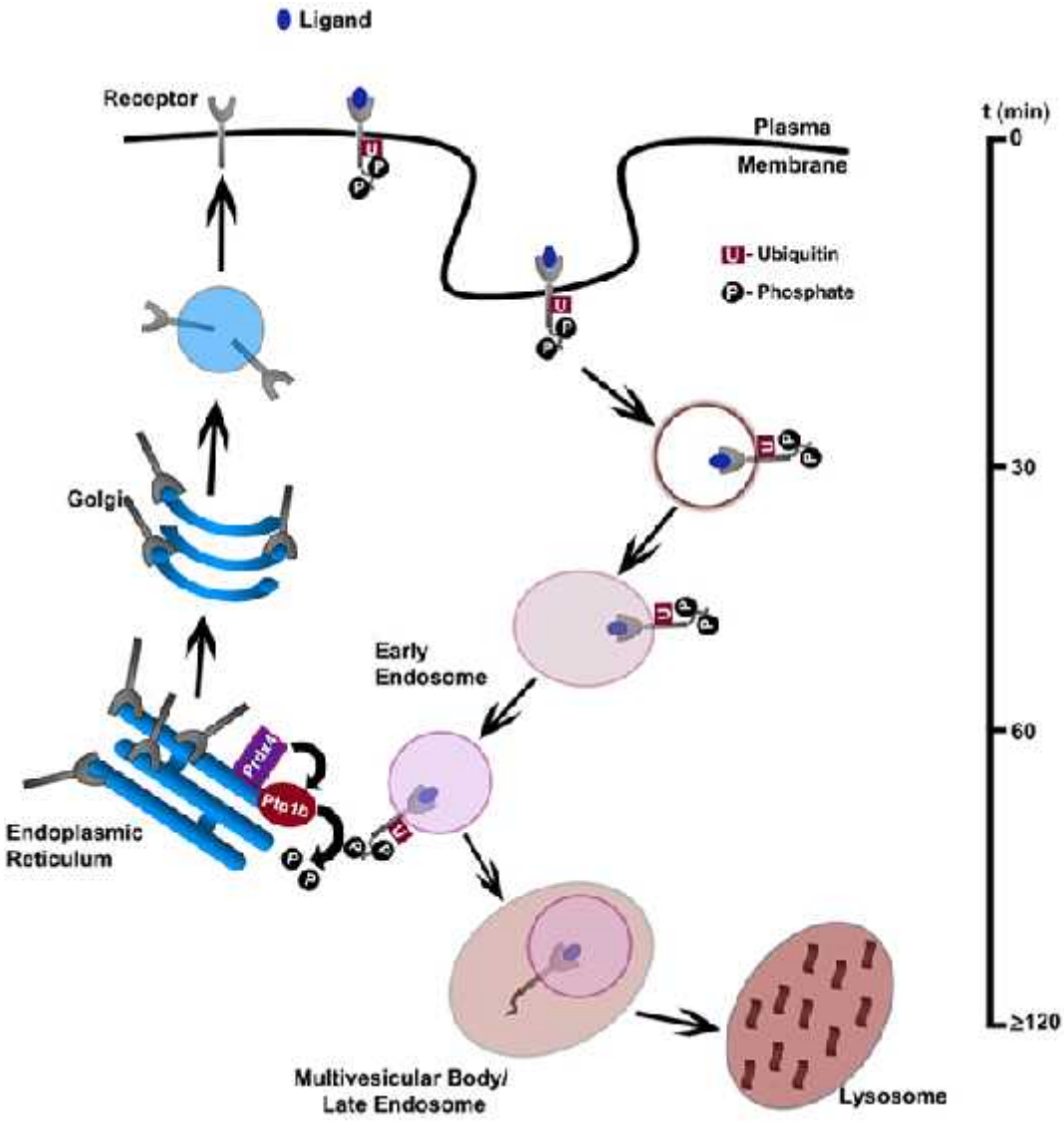

Figure 2. Model of CSF3R routing and involvement of Prdx4/Ptp1b at the ER-early endosome interface. After ligand-induced activation and internalization, CSF3R will enter the early endosome compartment, where signaling continues. The CSF3R present in the early (signaling) endosomes are subject to two major modulatory mechanisms which are interdependent (see main text): (1) targeting to multivesicular bodies/late endosomes resulting in lysosomal degradation, a process depending on the ubiqitination status of CSF3R-K632, controlled by SOCS3 and DUB2A; and (2) dephosphorylation by ER-resident Ptp1b, a redox sensitive protein tyrosine phosphatase, the activity of which is enhanced by the ER-resident antioxidant Prdx4. Possibly, although not yet shown, Prdx4/Ptp1b may also keep ER-resident CSF3R in the biosynthetic pathway in a dephosphorylated state. The time line provides a global indication of the temporal aspects of CSF3R trafficking in the retrograde pathway.

elevated plasma membrane expression and (v) give rise to elevated ROS levels (142). The increased generation of ROS by the CSF3R truncation mutant may be the direct consequence of their hampered endocytosis resulting in the loss of control of ROS levels by Prdx4 at the signaling endosome-ER interface. The significance of ER-resident Prdx4/Ptp1b in controlling myeloid homeostasis is further supported by the observation that Prdx4 is epigenetically down regulated in acute promyelocytic leukemia (APL), which may explain why APL cells are hyper responsive to CSF3 (128).

9. PERSPECTIVE

CSF3 has major therapeutic applications, ranging from the mobilization of stem cells for transplantation purposes in healthy donors to the alleviation of neutropenia in patients with severe congenital neutropenia or to circumvent febrile neutropenia in cancer patients undergoing chemotherapy. In experimental models, CSF3 also has therapeutic potential in ischemic myocardial or brain infarctions, muscle regeneration and neurodegenerative conditions, which may expand its

clinical application in the future even further (143, 144, 145, 146). Studies in SCN suggest that abnormal function of CSF3R, caused by mutations that prevent their normal intracellular trafficking, may contribute to a premalignant state of hematopoietic stem and progenitor cells. Elucidation of the mechanisms involved in CSF3R routing and their significance for the appropriate control of CSF3 signaling will help to better assess the risks and to further improve the benefits of the clinical usage of CSF3. This particularly applies to neutropenia patients who need life-long CSF3 treatment and are at high risk of developing AML. Unraveling the intricate regulatory network of myeloid cell proliferation, survival and differentiation may also shed further light on the complex pathogenesis of these myeloid disorders.

From a more general biological point of view, the challenge is to obtain full understanding of the signaling diversity from different cytokine receptor systems in relation to intracellular trafficking and to identify the critical regulators involved herein. At least some of these regulators appear to combine these functions. For instance, in this review SOCS3 has been put forward as an illustration of a direct regulator of receptor signaling (via its kinase inhibitory region) and of intracellular trafficking (via its SOCS-box). The protein tyrosine phosphatase PTP1B is another example of a dual regulator of signaling and endocytotic routing: While initially identified as a phosphatase involved in tyrosine kinase receptor dephosphorylation, PTP1B has more recently also been shown to be important for early endosome fusion, receptor trafficking and multivesicular body formation (147, 148). Although the general principles of the signaling-routing connections for receptor tyrosine kinases EGFR and PDGFR are gradually becoming clear, it will take considerably more effort to get insight into the full spectrum of variations on the theme for other receptor systems. This particularly applies to the cytokine receptors, which are expressed at much lower densities at the cell surface and in signaling endosomes than receptor tyrosine kinases and are often heteromeric. Because endocytotic routing largely depends on low-affinity ubiquitin-mediated interactions between cargo and the endocytotic machinery (e.g., ESCRTs), it is conceivable that accumulation of cytokine receptors in microdomains is first needed to obtain sufficiently high local concentrations for interactions with the ESCRTs. Recent advances in imaging and proteomics technologies may help to determine which proteins complexes are crucially involved in the dynamic interplay between cytokine receptor routing and signaling, and to assess what the level of heterogeneity and commonality between different receptor systems will be.

10. ACKNOWLEDGMENT

This work was supported by the Dutch Cancer Society “KWF kankerbestrijding” (KP, AM, IPT) and the EU-FP6 Marie Curie Research Training Network “Recepteur” (TJ, IPT).

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Key Words: CSF3 receptor, Signal transduction, JAK/STAT signaling, Intracellular trafficking, Suppressor of cytokine signaling, Deubiquitinating enzymes, Peroxiredoxin, Signaling endosome, Protein tyrosine phosphatase 1b, Review

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